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(54) Title: METHOD OF REGULATING NITRIC OXIDE PRODUCTION

(57) Abstract

Methods for regulating levels of nitric oxide are disclosed. The methods utilize IL–17 receptors, which may be used in conjunction with inhibitors of IL–1 and/or TNF.

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TITLE

METHOD OF REGULATING NITRIC OXIDE PRODUCTION

TECHNICAL FIELD OF THE INVENTION

The present invention relates generally to the modulation of levels of nitric oxide, particularly in osteoarthritis.

BACKGROUND OF THE INVENTION

Cytokines are hormone-like molecules that regulate various aspects of an immune or inflammatory response; they exert their effects by specifically binding receptors present on cells, and transducing a signal to the cells. In addition to having beneficial effects (i.e., development of an effective immune response and control of infectious disease), cytokines have also been implicated in various autoimmune and inflammatory conditions.

Various cartilage associated cells (i.e., chondrocytes, synovial lining cells, endothelial cells, synovial fibroblasts and mononuclear cells that are present in a joint) can release nitric oxide (NO). This free radical serves as a front-line antimicrobial agent and also has antitumor effects. However, NO has also been implicated in several deleterious conditions, including autoimmune and inflammatory diseases and the bone destruction that occurs in osteoarthritis, which is not typically thought of as an inflammatory condition.

Rouvier et al. (*J. Immunol.* 150:5445; 1993) reported a novel cDNA which they termed CTLA-8, and which has since become known as Interleukin-17 (IL-17). IL-17 is 57% homologous to the predicted amino acid sequence of an open reading frame (ORF) present in Herpesvirus saimiri (HSV) referred to as HVS13 (Nicholas et al. *Virol.* 179:1 89, 1990; Albrecht et al., *J. Virol.* 66:5047;1992).

A novel receptor that binds IL-17 and its viral homolog, HVS13, has been cloned as described in USSN 08/620,694, filed March 21, 1996. The receptor is a Type I transmembrane protein; the mouse receptor has 864 amino acid residues, the human receptor has 866 amino acid residues. A soluble form of the receptor was found to inhibit various IL-17-mediated activities.

SUMMARY OF THE INVENTION

Nitric oxide (NO) is a free radical that is involved in many phenomena, including the pathophysiological conditions of rheumatoid arthritis (RA) and osteoarthritis (OA). IL-17 stimulates production of NO by cartilage from individuals afflicted with OA. A soluble form of IL-17R was found to inhibit various IL-17-mediated activities. Accordingly, soluble IL-17R will be useful in regulating levels of NO in a clinical setting.

DETAILED DESCRIPTION OF THE INVENTION

Nitric oxide is an intracellular signaling molecule that is involved in many physiological phenomena, including endothelium-dependent relaxation, neurotransmission and cell-mediated immune responses. As an antimicrobial agent, NO is effective against bacteria, viruses, helminths and parasites; it is also useful in the killing of tumor cells. Increased levels of NO occur in inflammatory disease (i.e., arthritis, ulcerative colitis, diabetes, Crohn's disease), and inhibitors of NO synthetases (NOS) have been used in experimental models of inflammatory disease, with varied effects (reviewed by A.O. Vladutiu in *Clinical Immunology and Immunopathology* 76:1-11; 1995).

Osteoarthritis (OA) has typically been considered a non-inflammatory disease, however, Amin et al. (*J. Exp. Med.* 182:2097; 1995) recently reported that the levels of NOS are upregulated in cartilage from OA patients. Incubation of OA-affected cartilage in serum-free medium resulted in the spontaneous release of substantial amounts of NO. Interleukin-1ß (IL-1ß), tumor necrosis factor-α (TNF-α) and lipopolysaccharide (LPS) augmented the nitrite release of OA-affected cartilage. Similar results were observed by Sakurai et al. (*J. Clin. Invest.* 96:2357, 1995) for rheumatoid arthritis patients.

IL-17 also upregulates release of NO from OA-affected cartilage. Moreover, inhibitors of IL-1ß and TNF-α do not inhibit the IL-17-augmented release of NO. Accordingly, inhibitors of IL-17 will be useful in regulating levels of NO. Such inhibitors will find therapeutic application in ameliorating the effects of NO in OA, as well as in other disease conditions in which this free radical plays a role (i.e., autoimmune and inflammatory disease).

A particularly preferred form of IL-17 inhibitor is soluble IL-17R, which is described in detail in USSN 08/620,694. IL-17 inhibitors may be used in conjunction with (i.e., simultaneously, separately or sequentially) inhibitors of IL-1 and TNF. Exemplary IL-1 inhibitors include soluble IL-1 receptors such as those described in U.S. Patents 5,319,071, 5,180,812 and 5,350,683, as well as a protein known as IL-1 receptor antagonist (IL-1RA; Eisenberg et al., *Nature* 343:341, 1990) and inhibitors of an enzyme that cleaves IL-1 into its biologically active form, as described in U.S. Patent 5,416,013.

Exemplary TNF inhibitors include soluble forms of TNF receptors, for example as described in U.S. Patent 5,395,760, and TNF receptor fusion proteins such as those disclosed in USSN 08/406,824 and USSN 08/651,286. In additional, certain virally-encoded proteins are known to bind TNF and act as TNF antagonists, as described in U.S. Patents 5,359,039 and 5,464,938; and inhibitors of an enzyme that cleaves TNF into its biologically active form are also known (see USSN 08/651,363 and USSN 08/655,345).

The relevant disclosures of the aforementioned patents and patent applications are incorporated by reference herein.

IL-17, HVS13 and homologous proteins

CTLA-8 refers to a cDNA cloned from an activated T cell hybridoma clone (Rouvier et al., *J. Immunol.* 150:5445; 1993). Northern blot analysis indicated that CTLA-8 transcription was very tissue specific. The CTLA-8 gene was found to map at chromosomal site 1a in mice, and at 2q31 in humans. Although a protein encoded by the CTLA-8 gene was never identified by Rouvier et al, the predicted amino acid sequence of CTLA-8 was found to be 57% homologous to the predicted amino acid sequence of an ORF present in Herpesvirus Saimiri, HVS13. The CTLA-8 protein is referred to herein as Interleukin-17 (IL-17).

The complete nucleotide sequence of the genome of HVS has been reported (Albrecht et al., *J. Virol.* 66:5047; 1992). Additional studies on one of the HVS open reading frames (ORFs), HVS13, are described in Nicholas et al., *Virol.* 179:1 89; 1990. HVS13 is a late gene which is present in the Hind III-G fragment of HVS. Antisera developed against peptides derived from HVS13 are believed to react with a late protein (Nicholas et al., *supra*).

As described USSN 08/462,353, a CIP of USSN 08/410,536, filed March 23, 1995, full length murine CTLA-8 protein and a CTLA-8/Fc fusion protein were expressed, tested, and found to act as a costimulus for the proliferation of T cells. Human IL-17 (CTLA-8) was identified by probing a human T cell library using a DNA fragment derived from degenerate PCR; homologs of IL-17 (CTLA-8) are expected to exist in other species as well. A full length HVS13 protein, as well as an HVS13/Fc fusion protein, were also expressed, and found to act in a similar manner to IL-17 (CTLA-8) protein. Moreover, other species of herpesviruses are also likely to encode proteins homologous to that encoded by HVS13.

Proteins and Analogs

USSN 08/620,694, filed March 21, 1996, discloses isolated IL-17R and homologs thereof having immunoregulatory activity. Such proteins are substantially free of contaminating endogenous materials and, optionally, without associated native-pattern glycosylation. Derivatives of IL-17R within the scope of the invention also include various structural forms of the primary protein which retain biological activity. Due to the presence of ionizable amino and carboxyl groups, for example, an IL-17R protein may be in the form of acidic or basic salts, or may be in neutral form. Individual amino acid residues may also be modified by oxidation or reduction.

The primary amino acid structure may be modified by forming covalent or aggregative conjugates with other chemical moieties, such as glycosyl groups, lipids, phosphate, acetyl groups and the like, or by creating amino acid sequence mutants. Covalent derivatives are prepared by linking particular functional groups to amino acid side chains or at the N- or C-termini.

Soluble forms of IL-17R are also within the scope of the invention. The nucleotide and predicted amino acid sequence of the murine IL-17R is shown in SEQ ID NOs:1 and 2. Computer analysis indicated that the protein has an N-terminal signal peptide with a cleavage site between amino acid 31 and 32. Those skilled in the art will recognize that the actual cleavage site may be different than that predicted by computer analysis. Thus, the N-terminal amino acid of the cleaved peptide is expected to be within about five amino acids on either side of the predicted cleavage site. The signal peptide is followed by a 291 amino acid extracellular domain, a 21 amino acid transmembrane domain, and a 521 amino acid cytoplasmic tail. Soluble IL-17R comprises the signal peptide and the extracellular domain (residues 1 to 322 of SEQ ID N0:1) or a fragment thereof. Alternatively, a different signal peptide can be substituted for residues 1 through 31 of SEQ ID NO:1.

The nucleotide and predicted amino acid sequence of the human IL-17R is shown in SEQ ID NOs:3 and 4. It shares many features with the murine IL-17 R. Computer analysis indicated that the protein has an N-terminal signal peptide with a cleavage site between amino acid 27 and 28. Those skilled in the art will recognize that the actual cleavage site may be different than that predicted by computer analysis. Thus, the N-terminal amino acid of the cleaved peptide is expected to be within about five amino acids on either side of the predicted cleavage site. The signal peptide is followed by a 293 amino acid extracellular domain, a 21 amino acid transmembrane domain, and a 525 amino acid cytoplasmic tail. Soluble IL-17R comprises the signal peptide and the extracellular domain (residues 1 to 320 of SEQ ID N0:1) or a fragment thereof. Alternatively, a different signal peptide can be substituted for the native signal peptide.

Other derivatives of the IL-17R protein and homologs thereof within the scope of this invention include covalent or aggregative conjugates of the protein or its fragments with other proteins or polypeptides, such as by synthesis in recombinant culture as N-terminal or C-terminal fusions. For example, the conjugated peptide may be a signal (or leader) polypeptide sequence at the N-terminal region of the protein which co-translationally or post-translationally directs transfer of the protein from its site of synthesis to its site of function inside or outside of the cell membrane or wall (e.g., the yeast α-factor leader).

Protein fusions can comprise peptides added to facilitate purification or identification of IL-17R proteins and homologs (e.g., poly-His). The amino acid sequence of the inventive proteins can also be linked to an identification peptide such as that

described by Hopp et al., *Bio/Technology* 6:1204 (1988). Such a highly antigenic peptide provides an epitope reversibly bound by a specific monoclonal antibody, enabling rapid assay and facile purification of expressed recombinant protein. The sequence of Hopp et al. is also specifically cleaved by bovine mucosal enterokinase, allowing removal of the peptide from the purified protein. Fusion proteins capped with such peptides may also be resistant to intracellular degradation in *E. coli*.

Soluble forms of some transmembrane proteins have been expressed as fusion proteins in which an extracellular domain of a membrane protein (cognate binding region) is joined to an immunoglobulin heavy chain constant (Fc) domain. Such fusion proteins are useful as reagents to detect their cognate proteins. They are also useful as therapeutic agents in treatment of disease. However, receptors for Fc domains are present on many cell types. Thus, when a fusion protein is formed from an Fc domain and a cognate binding region, binding to a cell may occur either through binding of the cognate binding region to its cognate protein, or through binding of the Fc domain to an Fc receptor (FcR). Such binding of the Fc domain to Fc receptors may overwhelm any binding of the cognate binding region to its cognate. Moreover, binding of Fc domains to Fc receptors induces secretion of various cytokines that are involved in upregulating various aspects of an immune or inflammatory response; such upregulation has been implicated in some of the adverse effects of therapeutic administration of certain antibodies (Krutman et al., *J. Immunol.* 145:1337, 1990; Thistlewaite et al., *Am. J. Kidney Dis.* 11:112, 1988).

Jefferis et al. (*Mol. Immunol.* 27:1237; 1990) reported that a region of an antibody referred to as the hinge region (and specifically residues 234-237 within this region) determine recognition of the antibody by human Fc receptors FcγRI, FcγRII, and FcγRIII. $Leu_{(234)}$ and $Leu_{(235)}$ were critical to high affinity binding of IgG_3 to FcγRI present on U937 cells (Canfield and Morrison, *J. Exp. Med.* 173:1483; 1991). Similar results were obtained by Lund et al. (*J. Immunol.* 147:2657, 1991; *Molecular Immunol.* 29:53, 1991). These authors observed 10-100 fold decrease in affinity of IgG for FcR when a single amino acid substitution was made at a critical residue.

A single amino acid substitution in the Fc domain of an anti-CD3 monoclonal antibody (leucine to glutamic acid at position 235) was found to result in significantly less T cell activation than unmutagenized antibody, while maintaining the immunosuppressive properties (Alegre et al., *J. Immunol.* 148:3461; 1992). Wawrzynczak et al. found that murine monoclonal antibodies that contained a single amino acid substitution at residue 235 had the same serum half-life as did native antibodies (*Mol. Immunol.* 29:221; 1992). Fc domains with reduced affinity for Fc receptors are useful in the preparation of Fc fusion proteins.

Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., *Science* 240:1759, 1988). Leucine zipper domain is a term used to refer to a conserved peptide domain present in these (and other) proteins, which is responsible for dimerization of the proteins. The leucine zipper domain (also referred to herein as an oligomerizing, or oligomer-forming, domain) comprises a repetitive heptad repeat, with four or five leucine residues interspersed with other amino acids. Examples of leucine zipper domains are those found in the yeast transcription factor GCN4 and a heat-stable DNA-binding protein found in rat liver (C/EBP; Landschulz et al., *Science* 243:1681, 1989). Two nuclear transforming proteins, *fos* and *jun*, also exhibit leucine zipper domains, as does the gene product of the murine proto-oncogene, *c-myc* (Landschulz et al., *Science* 240:1759, 1988). The products of the nuclear oncogenes *fos* and *jun* comprise leucine zipper domains preferentially form a heterodimer (O'Shea et al., *Science* 245:646, 1989; Turner and Tjian, *Science* 243:1689, 1989). The leucine zipper domain is necessary for biological activity (DNA binding) in these proteins.

The fusogenic proteins of several different viruses, including paramyxovirus, coronavirus, measles virus and many retroviruses, also possess leucine zipper domains (Buckland and Wild, *Nature* 338:547,1989; Britton, *Nature* 353:394, 1991; Delwart and Mosialos, *AIDS Research and Human Retroviruses* 6:703, 1990). The leucine zipper domains in these fusogenic viral proteins are near the transmembrane region of the proteins; it has been suggested that the leucine zipper domains could contribute to the oligomeric structure of the fusogenic proteins. Oligomerization of fusogenic viral proteins is involved in fusion pore formation (Spruce et al, *Proc. Natl. Acad. Sci. U.S.A.* 88:3523, 1991). Leucine zipper domains have also been recently reported to play a role in oligomerization of heat-shock transcription factors (Rabindran et al., *Science* 259:230, 1993).

Leucine zipper domains fold as short, parallel coiled coils. (O'Shea et al., *Science* 254:539; 1991) The general architecture of the parallel coiled coil has been well characterized, with a "knobs-into-holes" packing as proposed by Crick in 1953 (*Acta Crystallogr.* 6:689). The dimer formed by a leucine zipper domain is stabilized by the heptad repeat, designated $(abcdefg)_n$ according to the notation of McLachlan and Stewart (*J. Mol. Biol.* 98:293; 1975), in which residues *a* and *d* are generally hydrophobic residues, with *d* being a leucine, which line up on the same face of a helix. Oppositely-charged residues commonly occur at positions *g* and *e*. Thus, in a parallel coiled coil formed from two helical leucine zipper domains, the "knobs" formed by the hydrophobic side chains of the first helix are packed into the "holes" formed between the side chains of the second helix.

The leucine residues at position *d* contribute large hydrophobic stabilization energies, and are important for dimer formation (Krystek et al., *Int. J. Peptide Res.*

38:229, 1991). Lovejoy et al. recently reported the synthesis of a triple-stranded α-helical bundle in which the helices run up-up-down (*Science* 259:1288, 1993). Their studies confirmed that hydrophobic stabilization energy provides the main driving force for the formation of coiled coils from helical monomers. These studies also indicate that electrostatic interactions contribute to the stoichiometry and geometry of coiled coils.

Several studies have indicated that conservative amino acids may be substituted for individual leucine residues with minimal decrease in the ability to dimerize; multiple changes, however, usually result in loss of this ability (Landschulz et al., *Science* 243:1681, 1989; Turner and Tjian, *Science* 243:1689, 1989; Hu et al., *Science* 250:1400, 1990). van Heekeren et al. reported that a number of different amino residues can be substituted for the leucine residues in the leucine zipper domain of GCN4, and further found that some GCN4 proteins containing two leucine substitutions were weakly active (*Nucl. Acids Res.* 20:3721, 1992). Mutation of the first and second heptadic leucines of the leucine zipper domain of the measles virus fusion protein (MVF) did not affect syncytium formation (a measure of virally-induced cell fusion); however, mutation of all four leucine residues prevented fusion completely (Buckland et al., *J. Gen. Virol.* 73:1703, 1992). None of the mutations affected the ability of MVF to form a tetramer.

Recently, amino acid substitutions in the *a* and *d* residues of a synthetic peptide representing the GCN4 leucine zipper domain have been found to change the oligomerization properties of the leucine zipper domain (Alber, Sixth Symposium of the Protein Society, San Diego, CA). When all residues at position *a* are changed to isoleucine, the leucine zipper still forms a parallel dimer. When, in addition to this change, all leucine residues at position *d* are also changed to isoleucine, the resultant peptide spontaneously forms a trimeric parallel coiled coil in solution. Substituting all amino acids at position *d* with isoleucine and at position *a* with leucine results in a peptide that tetramerizes. Peptides containing these substitutions are still referred to as leucine zipper domains since the mechanism of oligomer formation is believed to be the same as that for traditional leucine zipper domains such as those described above.

Derivatives of IL-17R may also be used as immunogens, reagents in *in vitro* assays, or as binding agents for affinity purification procedures. Such derivatives may also be obtained by cross-linking agents, such as M-maleimidobenzoyl succinimide ester and N-hydroxysuccinimide, at cysteine and lysine residues. The inventive proteins may also be covalently bound through reactive side groups to various insoluble substrates, such as cyanogen bromide-activated, bisoxirane-activated, carbonyldiimidazole-activated or tosyl-activated agarose structures, or by adsorbing to polyolefin surfaces (with or without glutaraldehyde cross-linking). Once bound to a substrate, proteins may be used to selectively bind (for purposes of assay or purification) antibodies raised against the IL-17R

or against other proteins which are similar to the IL-17R, as well as other proteins that bind IL-17R or its homologous proteins.

The present invention also includes IL-17R with or without associated native-pattern glycosylation. Proteins expressed in yeast or mammalian expression systems, e.g., COS-7 cells, may be similar or slightly different in molecular weight and glycosylation pattern than the native molecules, depending upon the expression system. Expression of DNAs encoding the inventive proteins in bacteria such as *E. coli* provides non-glycosylated molecules. Functional mutant analogs of IL-17R protein or homologs thereof having inactivated N-glycosylation sites can be produced by oligonucleotide synthesis and ligation or by site-specific mutagenesis techniques. These analog proteins can be produced in a homogeneous, reduced-carbohydrate form in good yield using yeast expression systems. N-glycosylation sites in eukaryotic proteins are characterized by the amino acid triplet Asn-A_1-Z, where A_1 is any amino acid except Pro, and Z is Ser or Thr. In this sequence, asparagine provides a side chain amino group for covalent attachment of carbohydrate. Such a site can be eliminated by substituting another amino acid for Asn or for residue Z, deleting Asn or Z, or inserting a non-Z amino acid between A_1 and Z, or an amino acid other than Asn between Asn and A_1.

IL-17R protein derivatives may also be obtained by mutations of the native IL-17R or its subunits. A IL-17R mutated protein, as referred to herein, is a polypeptide homologous to a IL-17R protein but which has an amino acid sequence different from the native IL-17R because of one or a plurality of deletions, insertions or substitutions. The effect of any mutation made in a DNA encoding a IL-17R peptide may be easily determined by analyzing the ability of the mutated IL-17R peptide to inhibit costimulation of T or B cells by IL-17 (CTLA-8) or homologous proteins, or to bind proteins that specifically bind IL-17R (for example, antibodies or proteins encoded by the CTLA-8 cDNA or the HVS13 ORF). Moreover, activity of IL-17R analogs, muteins or derivatives can be determined by any of the assays methods described herein. Similar mutations may be made in homologs of IL-17R, and tested in a similar manner.

Bioequivalent analogs of the inventive proteins may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine residues can be deleted or replaced with other amino acids to prevent formation of incorrect intramolecular disulfide bridges upon renaturation. Other approaches to mutagenesis involve modification of adjacent dibasic amino acid residues to enhance expression in yeast systems in which KEX2 protease activity is present.

Generally, substitutions should be made conservatively; i.e., the most preferred substitute amino acids are those which do not affect the ability of the inventive proteins to

bind their ligands in a manner substantially equivalent to that of native mIL-17R or hIL-17R. Examples of conservative substitutions include substitution of amino acids outside of the binding domain(s), and substitution of amino acids that do not alter the secondary and/or tertiary structure of IL-17R and homologs thereof. Additional examples include substituting one aliphatic residue for another, such as Ile, Val, Leu, or Ala for one another, or substitutions of one polar residue for another, such as between Lys and Arg; Glu and Asp; or Gln and Asn. Other such conservative substitutions, for example, substitutions of entire regions having similar hydrophobicity characteristics, are well known.

Similarly, when a deletion or insertion strategy is adopted, the potential effect of the deletion or insertion on biological activity should be considered. Subunits of the inventive proteins may be constructed by deleting terminal or internal residues or sequences. Fragments of IL-17R that bind IL-17 can be readily prepared (for example, by using restriction enzymes to delete portions of the DNA) and tested for their ability to bind IL-17. Additional guidance as to the types of mutations that can be made is provided by a comparison of the sequence of IL-17R to proteins that have similar structures, as well as by performing structural analysis of the inventive proteins.

Mutations in nucleotide sequences constructed for expression of analog IL-17R must, of course, preserve the reading frame phase of the coding sequences and preferably will not create complementary regions that could hybridize to produce secondary mRNA structures such as loops or hairpins which would adversely affect translation of the receptor mRNA. Although a mutation site may be predetermined, it is not necessary that the nature of the mutation *per se* be predetermined. For example, in order to select for optimum characteristics of mutants at a given site, random mutagenesis may be conducted at the target codon and the expressed mutated viral proteins screened for the desired activity.

Not all mutations in the nucleotide sequence which encodes a IL-17R protein or homolog thereof will be expressed in the final product, for example, nucleotide substitutions may be made to enhance expression, primarily to avoid secondary structure loops in the transcribed mRNA (see EPA 75,444A, incorporated herein by reference), or to provide codons that are more readily translated by the selected host, e.g., the well-known *E. coli* preference codons for *E. coli* expression.

Mutations can be introduced at particular loci by synthesizing oligonucleotides containing a mutant sequence, flanked by restriction sites enabling ligation to fragments of the native sequence. Following ligation, the resulting reconstructed sequence encodes an analog having the desired amino acid insertion, substitution, or deletion.

Alternatively, oligonucleotide-directed site-specific mutagenesis procedures can be employed to provide an altered gene having particular codons altered according to the substitution, deletion, or insertion required. Exemplary methods of making the alterations

set forth above are disclosed by Walder et al. (*Gene 42*:133, 1986); Bauer et al. (*Gene 37*:73, 1985); Craik (*BioTechniques*, January 1985, 12-19); Smith et al. (*Genetic Engineering: Principles and Methods*, Plenum Press, 1981); and U.S. Patent Nos. 4,518,584 and 4,737,462 disclose suitable techniques, and are incorporated by reference herein.

Due to code degeneracy, there can be considerable variation in nucleotide sequences encoding the same amino acid sequence. Other embodiments include sequences capable of hybridizing under moderately stringent conditions (prewashing solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0) and hybridization conditions of 50°C, 5 X SSC, overnight) to the DNA sequences encoding IL-17R, and other sequences which are degenerate to those which encode the IL-17R. In a preferred embodiment, IL-17R analogs are at least about 70 % identical in amino acid sequence to the amino acid sequence of IL-17R proteins as set forth in SEQ ID NO:1 or SEQ ID NO:3. Similarly, analogs of IL-17R homologs are at least about 70 % identical in amino acid sequence to the amino acid sequence of the native, homologous proteins. In a more preferred embodiment, analogs of IL-17R or homologs thereof are at least about 80 % identical in amino acid sequence to the native form of the inventive proteins; in a most preferred embodiment, analogs of IL-17R or homologs thereof are at least about 90 % identical in amino acid sequence to the native form of the inventive proteins.

Percent identity may be determined using a computer program, for example, the GAP computer program described by Devereux et al. (*Nucl. Acids Res.* 12:387, 1984) and available from the University of Wisconsin Genetics Computer Group (UWGCG). For fragments derived from the IL-17R protein, the identity is calculated based on that portion of the IL-17R protein that is present in the fragment. Similar methods can be used to analyze homologs of IL-17R.

The ability of IL-17R analogs to bind CTLA-8 can be determined by testing the ability of the analogs to inhibit IL-17 (CTLA-8) -induced T cell proliferation. Alternatively, suitable assays, for example, an enzyme immunoassay or a dot blot, employing CTLA-8 or HSV13 (or a homolog thereof which binds native IL-17R) can be used to assess the ability of IL-17R analogs to bind CTLA-8. Such methods are well known in the art.

Expression of Recombinant Receptors for IL-17

The proteins of the present invention are preferably produced by recombinant DNA methods by inserting a DNA sequence encoding IL-17R protein or a homolog thereof into a recombinant expression vector and expressing the DNA sequence in a recombinant microbial expression system under conditions promoting expression. DNA sequences encoding the proteins provided by this invention can be assembled from cDNA fragments

and short oligonucleotide linkers, or from a series of oligonucleotides, to provide a synthetic gene which is capable of being inserted in a recombinant expression vector and expressed in a recombinant transcriptional unit.

Recombinant expression vectors include synthetic or cDNA-derived DNA fragments encoding IL-17R, homologs, or bioequivalent analogs, operably linked to suitable transcriptional or translational regulatory elements derived from mammalian, microbial, viral or insect genes. Such regulatory elements include a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable mRNA ribosomal binding sites, and sequences which control the termination of transcription and translation, as described in detail below. The ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants may additionally be incorporated.

DNA regions are operably linked when they are functionally related to each other. For example, DNA for a signal peptide (secretory leader) is operably linked to DNA for a polypeptide if it is expressed as a precursor which participates in the secretion of the polypeptide; a promoter is operably linked to a coding sequence if it controls the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to permit translation. Generally, operably linked means contiguous and, in the case of secretory leaders, contiguous and in reading frame. DNA sequences encoding IL-17R or homologs which are to be expressed in a microorganism will preferably contain no introns that could prematurely terminate transcription of DNA into mRNA.

Useful expression vectors for bacterial use can comprise a selectable marker and bacterial origin of replication derived from commercially available plasmids comprising genetic elements of the well known cloning vector pBR322 (ATCC 37017). Such commercial vectors include, for example, pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden) and pGEM1 (Promega Biotec, Madison, WI, USA). These pBR322 "backbone" sections are combined with an appropriate promoter and the structural sequence to be expressed. *E. coli* is typically transformed using derivatives of pBR322, a plasmid derived from an *E. coli* species (Bolivar et al., *Gene* 2:95, 1977). pBR322 contains genes for ampicillin and tetracycline resistance and thus provides simple means for identifying transformed cells.

Promoters commonly used in recombinant microbial expression vectors include the β-lactamase (penicillinase) and lactose promoter system (Chang et al., *Nature 275*:615, 1978; and Goeddel et al., *Nature 281*:544, 1979), the tryptophan (trp) promoter system (Goeddel et al., *Nucl. Acids Res. 8*:4057, 1980; and EPA 36,776) and tac promoter (Maniatis, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory, p.

412, 1982). A particularly useful bacterial expression system employs the phage λ P_L promoter and cI857ts thermolabile repressor. Plasmid vectors available from the American Type Culture Collection which incorporate derivatives of the λ P_L promoter include plasmid pHUB2, resident in *E. coli* strain JMB9 (ATCC 37092) and pPLc28, resident in *E. coli* RR1 (ATCC 53082).

Suitable promoter sequences in yeast vectors include the promoters for metallothionein, 3-phosphoglycerate kinase (Hitzeman et al., *J. Biol. Chem.* *255*:2073, 1980) or other glycolytic enzymes (Hess et al., *J. Adv. Enzyme Reg.* *7*:149, 1968; and Holland et al., *Biochem.* *17*:4900, 1978), such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase. Suitable vectors and promoters for use in yeast expression are further described in R. Hitzeman et al., EPA 73,657.

Preferred yeast vectors can be assembled using DNA sequences from pBR322 for selection and replication in *E. coli* (Amp^r gene and origin of replication) and yeast DNA sequences including a glucose-repressible ADH2 promoter and α-factor secretion leader. The ADH2 promoter has been described by Russell et al. (*J. Biol. Chem.* *258*:2674, 1982) and Beier et al. (*Nature* *300*:724, 1982). The yeast α-factor leader, which directs secretion of heterologous proteins, can be inserted between the promoter and the structural gene to be expressed. *See, e.g.*, Kurjan et al., *Cell* *30*:933, 1982; and Bitter et al., *Proc. Natl. Acad. Sci. USA* *81*:5330, 1984. The leader sequence may be modified to contain, near its 3' end, one or more useful restriction sites to facilitate fusion of the leader sequence to foreign genes.

The transcriptional and translational control sequences in expression vectors to be used in transforming vertebrate cells may be provided by viral sources. For example, commonly used promoters and enhancers are derived from Polyoma, Adenovirus 2, Simian Virus 40 (SV40), and human cytomegalovirus. DNA sequences derived from the SV40 viral genome, for example, SV40 origin, early and late promoter, enhancer, splice, and polyadenylation sites may be used to provide the other genetic elements required for expression of a heterologous DNA sequence. The early and late promoters are particularly useful because both are obtained easily from the virus as a fragment which also contains the SV40 viral origin of replication (Fiers et al., *Nature* *273*:113, 1978). Smaller or larger SV40 fragments may also be used, provided the approximately 250 bp sequence extending from the *Hind* III site toward the *Bgl*I site located in the viral origin of replication is included. Further, viral genomic promoter, control and/or signal sequences may be utilized, provided such control sequences are compatible with the host cell chosen.

Exemplary vectors can be constructed as disclosed by Okayama and Berg (*Mol. Cell. Biol.* *3*:280, 1983).

A useful system for stable high level expression of mammalian receptor cDNAs in C127 murine mammary epithelial cells can be constructed substantially as described by Cosman et al. (*Mol. Immunol.* *23*:935, 1986). A preferred eukaryotic vector for expression of IL-17R DNA is referred to as pDC406 (McMahan et al., *EMBO J.* 10:2821, 1991), and includes regulatory sequences derived from SV40, human immunodeficiency virus (HIV), and Epstein-Barr virus (EBV). Other preferred vectors include pDC409 and pDC410, which are derived from pDC406. pDC410 was derived from pDC406 by substituting the EBV origin of replication with sequences encoding the SV40 large T antigen. pDC409 differs from pDC406 in that a *Bgl* II restriction site outside of the multiple cloning site has been deleted, making the *Bgl* II site within the multiple cloning site unique.

A useful cell line that allows for episomal replication of expression vectors, such as pDC406 and pDC409, which contain the EBV origin of replication, is CV-1/EBNA (ATCC CRL 10478). The CV-1/EBNA cell line was derived by transfection of the CV-1 cell line with a gene encoding Epstein-Barr virus nuclear antigen-1 (EBNA-1) and constitutively express EBNA-1 driven from human CMV immediate-early enhancer/promoter.

Host Cells

Transformed host cells are cells which have been transformed or transfected with expression vectors constructed using recombinant DNA techniques and which contain sequences encoding the proteins of the present invention. Transformed host cells may express the desired protein (IL-17R or homologs thereof), but host cells transformed for purposes of cloning or amplifying the inventive DNA do not need to express the protein. Expressed proteins will preferably be secreted into the culture supernatant, depending on the DNA selected, but may be deposited in the cell membrane.

Suitable host cells for expression of viral proteins include prokaryotes, yeast or higher eukaryotic cells under the control of appropriate promoters. Prokaryotes include gram negative or gram positive organisms, for example *E. coli* or *Bacillus* spp. Higher eukaryotic cells include established cell lines of mammalian origin as described below. Cell-free translation systems could also be employed to produce viral proteins using RNAs derived from the DNA constructs disclosed herein. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts are described by Pouwels et al. (*Cloning Vectors: A Laboratory Manual*, Elsevier, New York, 1985), the relevant disclosure of which is hereby incorporated by reference.

Prokaryotic expression hosts may be used for expression of IL-17R or homologs that do not require extensive proteolytic and disulfide processing. Prokaryotic expression vectors generally comprise one or more phenotypic selectable markers, for example a gene encoding proteins conferring antibiotic resistance or supplying an autotrophic requirement, and an origin of replication recognized by the host to ensure amplification within the host. Suitable prokaryotic hosts for transformation include *E. coli, Bacillus subtilis, Salmonella typhimurium*, and various species within the genera *Pseudomonas*, *Streptomyces*, and *Staphylococcus*, although others may also be employed as a matter of choice.

Recombinant IL-17R may also be expressed in yeast hosts, preferably from the *Saccharomyces* species, such as *S. cerevisiae*. Yeast of other genera, such as *Pichia* or *Kluyveromyces* may also be employed. Yeast vectors will generally contain an origin of replication from the 2μ yeast plasmid or an autonomously replicating sequence (ARS), promoter, DNA encoding the viral protein, sequences for polyadenylation and transcription termination and a selection gene. Preferably, yeast vectors will include an origin of replication and selectable marker permitting transformation of both yeast and *E. coli*, e.g., the ampicillin resistance gene of *E. coli* and *S. cerevisiae* trp1 gene, which provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, and a promoter derived from a highly expressed yeast gene to induce transcription of a structural sequence downstream. The presence of the trp1 lesion in the yeast host cell genome then provides an effective environment for detecting transformation by growth in the absence of tryptophan.

Suitable yeast transformation protocols are known to those of skill in the art; an exemplary technique is described by Hinnen et al., *Proc. Natl. Acad. Sci. USA 75*:1929, 1978, selecting for Trp^+ transformants in a selective medium consisting of 0.67% yeast nitrogen base, 0.5% casamino acids, 2% glucose, 10 μg/ml adenine and 20 μg/ml uracil. Host strains transformed by vectors comprising the ADH2 promoter may be grown for expression in a rich medium consisting of 1% yeast extract, 2% peptone, and 1% glucose supplemented with 80 μg/ml adenine and 80 μg/ml uracil. Derepression of the ADH2 promoter occurs upon exhaustion of medium glucose. Crude yeast supernatants are harvested by filtration and held at 4°C prior to further purification.

Various mammalian or insect cell culture systems can be employed to express recombinant protein. Baculovirus systems for production of heterologous proteins in insect cells are reviewed by Luckow and Summers, *Bio/Technology 6*:47 (1988). Examples of suitable mammalian host cell lines include the COS-7 lines of monkey kidney cells, described by Gluzman (*Cell 23*:175, 1981), and other cell lines capable of expressing an appropriate vector including, for example, CV-1/EBNA (ATCC CRL 10478), L cells, C127, 3T3, Chinese hamster ovary (CHO), HeLa and BHK cell lines. Mammalian

expression vectors may comprise nontranscribed elements such as an origin of replication, a suitable promoter and enhancer linked to the gene to be expressed, and other 5' or 3' flanking nontranscribed sequences, and 5' or 3' nontranslated sequences, such as necessary ribosome binding sites, a polyadenylation site, splice donor and acceptor sites, and transcriptional termination sequences.

Purification of Receptors for IL-17

Purified IL-17R, homologs, or analogs are prepared by culturing suitable host/vector systems to express the recombinant translation products of the DNAs of the present invention, which are then purified from culture media or cell extracts. For example, supernatants from systems which secrete recombinant protein into culture media can be first concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore Pellicon ultrafiltration unit.

Following the concentration step, the concentrate can be applied to a suitable purification matrix. For example, a suitable affinity matrix can comprise a counter structure protein or lectin or antibody molecule bound to a suitable support. Alternatively, an anion exchange resin can be employed, for example, a matrix or substrate having pendant diethylaminoethyl (DEAE) groups. The matrices can be acrylamide, agarose, dextran, cellulose or other types commonly employed in protein purification. Alternatively, a cation exchange step can be employed. Suitable cation exchangers include various insoluble matrices comprising sulfopropyl or carboxymethyl groups. Sulfopropyl groups are preferred. Gel filtration chromatography also provides a means of purifying the inventive proteins.

Affinity chromatography is a particularly preferred method of purifying IL-17R and homologs thereof. For example, a IL-17R expressed as a fusion protein comprising an immunoglobulin Fc region can be purified using Protein A or Protein G affinity chromatography. Moreover, a IL-17R protein comprising an oligomerizing zipper domain may be purified on a resin comprising an antibody specific to the oligomerizing zipper domain. Monoclonal antibodies against the IL-17R protein may also be useful in affinity chromatography purification, by utilizing methods that are well-known in the art. A ligand (i.e., IL-17 or HVS-13) may also be used to prepare an affinity matrix for affinity purification of IL-17R.

Finally, one or more reversed-phase high performance liquid chromatography (RP-HPLC) steps employing hydrophobic RP-HPLC media, e.g., silica gel having pendant methyl or other aliphatic groups, can be employed to further purify a IL-17R composition. Some or all of the foregoing purification steps, in various combinations, can also be employed to provide a homogeneous recombinant protein.

Recombinant protein produced in bacterial culture is usually isolated by initial extraction from cell pellets, followed by one or more concentration, salting-out, aqueous ion exchange or size exclusion chromatography steps. Finally, high performance liquid chromatography (HPLC) can be employed for final purification steps. Microbial cells employed in expression of recombinant viral protein can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents.

Fermentation of yeast which express the inventive protein as a secreted protein greatly simplifies purification. Secreted recombinant protein resulting from a large-scale fermentation can be purified by methods analogous to those disclosed by Urdal et al. (*J. Chromatog. 296*:171, 1984). This reference describes two sequential, reversed-phase HPLC steps for purification of recombinant human GM-CSF on a preparative HPLC column.

Protein synthesized in recombinant culture is characterized by the presence of cell components, including proteins, in amounts and of a character which depend upon the purification steps taken to recover the inventive protein from the culture. These components ordinarily will be of yeast, prokaryotic or non-human higher eukaryotic origin and preferably are present in innocuous contaminant quantities, on the order of less than about 1 percent by weight. Further, recombinant cell culture enables the production of the inventive proteins free of other proteins which may be normally associated with the proteins as they are found in nature in the species of origin.

Administration of IL-17R Compositions

The present invention provides methods of using therapeutic compositions comprising an effective amount of a protein and a suitable diluent and carrier. The use of IL-17R or homologs in conjunction with soluble cytokine receptors or cytokines, or other immunoregulatory molecules is also contemplated. Such molecules can be adminstered separaetly, sequentially or simulateously with IL-17R compositions. Particularaly preferred immunoregulatory moleculs are soluble IL-1 receptors, soluble TNF receptors, and fusion proteins thereof.

For therapeutic use, purified protein is administered to a patient, preferably a human, for treatment in a manner appropriate to the indication. Thus, for example, IL-17R protein compositions administered to regulate NO levels can be given by bolus injection, continuous infusion, sustained release from implants, or other suitable technique. Typically, a therapeutic agent will be administered in the form of a composition comprising purified IL-17R, in conjunction with physiologically acceptable carriers, excipients or

diluents. Such carriers will be nontoxic to recipients at the dosages and concentrations employed.

Ordinarily, the preparation of such protein compositions entails combining the inventive protein with buffers, antioxidants such as ascorbic acid, low molecular weight (less than about 10 residues) polypeptides, proteins, amino acids, carbohydrates including glucose, sucrose or dextrins, chelating agents such as EDTA, glutathione and other stabilizers and excipients. Neutral buffered saline or saline mixed with conspecific serum albumin are exemplary appropriate diluents. Preferably, product is formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose) as diluents. Appropriate dosages can be determined in trials. The amount and frequency of administration will depend, of course, on such factors as the nature and severity of the indication being treated, the desired response, the condition of the patient, and so forth.

Receptors for IL-17 (CTLA-8) can be administered for the purpose of regulating levels of NO. Soluble IL-17R are thus likely to be useful in treatment of osteoarthritis. The inventive receptor proteins will also be useful for prevention or treatment inflammation.

The following examples are offered by way of illustration, and not by way of limitation. Those skilled in the art will recognize that variations of the invention embodied in the examples can be made, especially in light of the teachings of the various references cited herein, the disclosures of which are incorporated by reference.

EXAMPLE 1

This example illustrates the ability of IL-17R to inhibit the proliferative response of T cells to mitogens. Lymphoid organs were harvested aseptically and cell suspension was created. Splenic and lymph node T cells were isolated from the cell suspension. The purity of the resulting splenic T cell preparations was routinely >95% $CD3^+$ and <1% $sIgM^+$. Purified murine splenic T cells (2×10^5/well) were cultured with either 1% PHA or 1 μg/ml Con A, and a soluble IL-17R (a soluble form of IL-17R comprising the extraceelular region of IL-17R fused to the Fc region of human IgG1) was titered into the assay. Proliferation was determined after 3 days with the addition of 1 μCi [^{3}H]thymidine. Secretion of cytokines (Interleukin-2) was determined for murine T cells cultured for 24 hr with 1 μg/ml of Con A in the presence or absence of 10 μg/ml of IL-17R.Fc or in the presence of a control Fc protein. IL-2 production was measured by ELISA and results expressed as ng/ml IL-2 produced.

Soluble IL-17R/Fc significantly inhibited the mitogen-induced proliferation of purified murine splenic T cells in a dose dependent manner, while a control Fc had no effect on the murine T cell proliferation. Complete inhibition of mitogen induced proliferation

was observed at a soluble IL-17R.Fc concentration of 10 μg/ml. Analysis of IL-2 production by splenic T cells activated with Con A in the presence or absence of IL-17R.Fc in the culture revealed that addition of IL-17R.Fc to the T-cell culture inhibited IL-2 production to levels 8-9-fold lower than those observed in cultures containing media alone or media plus a control Fc protein. Similar results were observed when purified human T cells were used.

EXAMPLE 2

This example illustrates the ability of IL-17R to inhibit the production of NO by cartilage-associated cells. Articular cartilage is obtained from OA-affected patients or normal controls substantially as described in Amin et al., supra. The cartilage is cut into small (approximately 3 mm) discs, which are placed in organ culture in the presence or absence of IL-17R.Fc or in the presence of a control Fc protein. Nitric oxide production is assayed by determining the nitrite level in the medium at different time intervals, for example by using a modified Griess reaction (*Anal. Biochem.* 12b:12299; 1982). Ding et al. (*J. Immunol.* 141:2407, 1988) also describe a useful method of measuring NO in *ex vivo* organ cultures of synovium and cartilage associated cells. The IL-17R.Fc is titrated to determine an effective concentration to inhibit NO production. Other soluble forms of IL-17R are also used to regulate NO levels in this manner.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Immunex Corporation

(ii) TITLE OF INVENTION:

(iii) NUMBER OF SEQUENCES: 4

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(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: Apple PowerMacintosh
(C) OPERATING SYSTEM: Apple Operating System 7.5.5
(D) SOFTWARE: Microsoft Word for PowerMacintosh, Version 6.0.1

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(viii) ATTORNEY/AGENT INFORMATION:
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(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 3288 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA to mRNA

(iii) HYPOTHETICAL: NO

(iv) ANTI-SENSE: NO

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(vi) ORIGINAL SOURCE:
      (A) ORGANISM: Mouse
      (B) CLONE: IL-17 receptor

(ix) FEATURE:
      (A) NAME/KEY: CDS
      (B) LOCATION: 121..2712

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

GTCGACTGGA ACGAGACGAC CTGCTGCCGA CGAGCGCCAG TCCTCGGCCG GGAAAGCCAT   60

CGCGGGCCCT CGCTGTCGCG CGGAGCCAGC TGCGAGCGCT CCGCGACCGG GCCGAGGGCT  120

ATG GCG ATT CGG CGC TGC TGG CCA CGG GTC GTC CCC GGG CCC GCG CTG    168
Met Ala Ile Arg Arg Cys Trp Pro Arg Val Val Pro Gly Pro Ala Leu
  1               5                  10                  15

GGA TGG CTG CTT CTG CTG CTG AAC GTT CTG GCC CCG GGC CGC GCC TCC    216
Gly Trp Leu Leu Leu Leu Leu Asn Val Leu Ala Pro Gly Arg Ala Ser
             20                  25                  30

CCG CGC CTC CTC GAC TTC CCG GCT CCG GTC TGC GCG CAG GAG GGG CTG    264
Pro Arg Leu Leu Asp Phe Pro Ala Pro Val Cys Ala Gln Glu Gly Leu
         35                  40                  45

AGC TGC AGA GTC AAG AAT AGT ACT TGT CTG GAT GAC AGC TGG ATC CAC    312
Ser Cys Arg Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
     50                  55                  60

CCC AAA AAC CTG ACC CCG TCT TCC CCA AAA AAC ATC TAT ATC AAT CTT    360
Pro Lys Asn Leu Thr Pro Ser Ser Pro Lys Asn Ile Tyr Ile Asn Leu
 65                  70                  75                  80

AGT GTT TCC TCT ACC CAG CAC GGA GAA TTA GTC CCT GTG TTG CAT GTT    408
Ser Val Ser Ser Thr Gln His Gly Glu Leu Val Pro Val Leu His Val
                 85                  90                  95

GAG TGG ACC CTG CAG ACA GAT GCC AGC ATC CTG TAC CTC GAG GGT GCA    456
Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
            100                 105                 110

GAG CTG TCC GTC CTG CAG CTG AAC ACC AAT GAG CGG CTG TGT GTC AAG    504
Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Lys
        115                 120                 125

TTC CAG TTT CTG TCC ATG CTG CAG CAT CAC CGT AAG CGG TGG CGG TTT    552
Phe Gln Phe Leu Ser Met Leu Gln His His Arg Lys Arg Trp Arg Phe
    130                 135                 140

TCC TTC AGC CAC TTT GTG GTA GAT CCT GGC CAG GAG TAT GAA GTG ACT    600
Ser Phe Ser His Phe Val Val Asp Pro Gly Gln Glu Tyr Glu Val Thr
145                 150                 155                 160

GTT CAC CAC CTG CCG AAG CCC ATC CCT GAT GGG GAC CCA AAC CAC AAA    648
Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Lys
                165                 170                 175
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TCC AAG ATC ATC TTT GTG CCT GAC TGT GAG GAC AGC AAG ATG AAG ATG      696
Ser Lys Ile Ile Phe Val Pro Asp Cys Glu Asp Ser Lys Met Lys Met
            180                 185                 190

ACT ACC TCA TGC GTG AGC TCA GGC AGC CTT TGG GAT CCC AAC ATC ACT      744
Thr Thr Ser Cys Val Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
        195                 200                 205

GTG GAG ACC TTG GAC ACA CAG CAT CTG CGA GTG GAC TTC ACC CTG TGG      792
Val Glu Thr Leu Asp Thr Gln His Leu Arg Val Asp Phe Thr Leu Trp
    210                 215                 220

AAT GAA TCC ACC CCC TAC CAG GTC CTG CTG GAA AGT TTC TCC GAC TCA      840
Asn Glu Ser Thr Pro Tyr Gln Val Leu Leu Glu Ser Phe Ser Asp Ser
225                 230                 235                 240

GAG AAC CAC AGC TGC TTT GAT GTC GTT AAA CAA ATA TTT GCG CCC AGG      888
Glu Asn His Ser Cys Phe Asp Val Val Lys Gln Ile Phe Ala Pro Arg
                245                 250                 255

CAA GAA GAA TTC CAT CAG CGA GCT AAT GTC ACA TTC ACT CTA AGC AAG      936
Gln Glu Glu Phe His Gln Arg Ala Asn Val Thr Phe Thr Leu Ser Lys
            260                 265                 270

TTT CAC TGG TGC TGC CAT CAC CAC GTG CAG GTC CAG CCC TTC TTC AGC      984
Phe His Trp Cys Cys His His His Val Gln Val Gln Pro Phe Phe Ser
        275                 280                 285

AGC TGC CTA AAT GAC TGT TTG AGA CAC GCT GTG ACT GTG CCC TGC CCA     1032
Ser Cys Leu Asn Asp Cys Leu Arg His Ala Val Thr Val Pro Cys Pro
    290                 295                 300

GTA ATC TCA AAT ACC ACA GTT CCC AAG CCA GTT GCA GAC TAC ATT CCC     1080
Val Ile Ser Asn Thr Thr Val Pro Lys Pro Val Ala Asp Tyr Ile Pro
305                 310                 315                 320

CTG TGG GTG TAT GGC CTC ATC ACA CTC ATC GCC ATT CTG CTG GTG GGA     1128
Leu Trp Val Tyr Gly Leu Ile Thr Leu Ile Ala Ile Leu Leu Val Gly
                325                 330                 335

TCT GTC ATC GTG CTG ATC ATC TGT ATG ACC TGG AGG CTT TCT GGC GCC     1176
Ser Val Ile Val Leu Ile Ile Cys Met Thr Trp Arg Leu Ser Gly Ala
            340                 345                 350

GAT CAA GAG AAA CAT GGT GAT GAC TCC AAA ATC AAT GGC ATC TTG CCC     1224
Asp Gln Glu Lys His Gly Asp Asp Ser Lys Ile Asn Gly Ile Leu Pro
        355                 360                 365

GTA GCA GAC CTG ACT CCC CCA CCC CTG AGG CCC AGG AAG GTC TGG ATC     1272
Val Ala Asp Leu Thr Pro Pro Pro Leu Arg Pro Arg Lys Val Trp Ile
    370                 375                 380

GTC TAC TCG GCC GAC CAC CCC CTC TAT GTG GAG GTG GTC CTA AAG TTC     1320
Val Tyr Ser Ala Asp His Pro Leu Tyr Val Glu Val Val Leu Lys Phe
385                 390                 395                 400

GCC CAG TTC CTG ATC ACT GCC TGT GGC ACT GAA GTA GCC CTT GAC CTC     1368
Ala Gln Phe Leu Ile Thr Ala Cys Gly Thr Glu Val Ala Leu Asp Leu
                405                 410                 415
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CTG GAA GAG CAG GTT ATC TCT GAG GTG GGG GTC ATG ACC TGG GTG AGC    1416
Leu Glu Glu Gln Val Ile Ser Glu Val Gly Val Met Thr Trp Val Ser
            420                 425                 430

CGA CAG AAG CAG GAG ATG GTG GAG AGC AAC TCC AAA ATC ATC ATC CTG    1464
Arg Gln Lys Gln Glu Met Val Glu Ser Asn Ser Lys Ile Ile Ile Leu
        435                 440                 445

TGT TCC CGA GGC ACC CAA GCA AAG TGG AAA GCT ATC TTG GGT TGG GCT    1512
Cys Ser Arg Gly Thr Gln Ala Lys Trp Lys Ala Ile Leu Gly Trp Ala
    450                 455                 460

GAG CCT GCT GTC CAG CTA CGG TGT GAC CAC TGG AAG CCT GCT GGG GAC    1560
Glu Pro Ala Val Gln Leu Arg Cys Asp His Trp Lys Pro Ala Gly Asp
465                 470                 475                 480

CTT TTC ACT GCA GCC ATG AAC ATG ATC CTG CCA GAC TTC AAG AGG CCA    1608
Leu Phe Thr Ala Ala Met Asn Met Ile Leu Pro Asp Phe Lys Arg Pro
                485                 490                 495

GCC TGC TTC GGC ACC TAC GTT GTT TGC TAC TTC AGT GGC ATC TGT AGT    1656
Ala Cys Phe Gly Thr Tyr Val Val Cys Tyr Phe Ser Gly Ile Cys Ser
            500                 505                 510

GAG AGG GAT GTC CCC GAC CTC TTC AAC ATC ACC TCC AGG TAC CCA CTC    1704
Glu Arg Asp Val Pro Asp Leu Phe Asn Ile Thr Ser Arg Tyr Pro Leu
        515                 520                 525

ATG GAC AGA TTT GAG GAG GTT TAC TTC CGG ATC CAG GAC CTG GAG ATG    1752
Met Asp Arg Phe Glu Glu Val Tyr Phe Arg Ile Gln Asp Leu Glu Met
    530                 535                 540

TTT GAA CCC GGC CGG ATG CAC CAT GTC AGA GAG CTC ACA GGG GAC AAT    1800
Phe Glu Pro Gly Arg Met His His Val Arg Glu Leu Thr Gly Asp Asn
545                 550                 555                 560

TAC CTG CAG AGC CCT AGT GGC CGG CAG CTC AAG GAG GCT GTG CTT AGG    1848
Tyr Leu Gln Ser Pro Ser Gly Arg Gln Leu Lys Glu Ala Val Leu Arg
                565                 570                 575

TTC CAG GAG TGG CAA ACC CAG TGC CCC GAC TGG TTC GAG CGT GAG AAC    1896
Phe Gln Glu Trp Gln Thr Gln Cys Pro Asp Trp Phe Glu Arg Glu Asn
            580                 585                 590

CTC TGC TTA GCT GAT GGC CAA GAT CTT CCC TCC CTG GAT GAA GAA GTG    1944
Leu Cys Leu Ala Asp Gly Gln Asp Leu Pro Ser Leu Asp Glu Glu Val
        595                 600                 605

TTT GAA GAC CCA CTG CTG CCA CCA GGG GGA GGA ATT GTC AAA CAG CAG    1992
Phe Glu Asp Pro Leu Leu Pro Pro Gly Gly Gly Ile Val Lys Gln Gln
    610                 615                 620

CCC CTG GTG CGG GAA CTC CCA TCT GAC GGC TGC CTT GTG GTA GAT GTC    2040
Pro Leu Val Arg Glu Leu Pro Ser Asp Gly Cys Leu Val Val Asp Val
625                 630                 635                 640

TGT GTC AGT GAG GAA GAA AGT AGA ATG GCA AAG CTG GAC CCT CAG CTA    2088
Cys Val Ser Glu Glu Glu Ser Arg Met Ala Lys Leu Asp Pro Gln Leu
                645                 650                 655
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TGG CCA CAG AGA GAG CTA GTG GCT CAC ACC CTC CAA AGC ATG GTG CTG   2136
Trp Pro Gln Arg Glu Leu Val Ala His Thr Leu Gln Ser Met Val Leu
            660                 665                 670

CCA GCA GAG CAG GTC CCT GCA GCT CAT GTG GTG GAG CCT CTC CAT CTC   2184
Pro Ala Glu Gln Val Pro Ala Ala His Val Val Glu Pro Leu His Leu
        675                 680                 685

CCA GAC GGC AGT GGA GCA GCT GCC CAG CTG CCC ATG ACA GAG GAC AGC   2232
Pro Asp Gly Ser Gly Ala Ala Ala Gln Leu Pro Met Thr Glu Asp Ser
    690                 695                 700

GAG GCT TGC CCG CTG CTG GGG GTC CAG AGG AAC AGC ATC CTT TGC CTC   2280
Glu Ala Cys Pro Leu Leu Gly Val Gln Arg Asn Ser Ile Leu Cys Leu
705                 710                 715                 720

CCC GTG GAC TCA GAT GAC TTG CCA CTC TGT AGC ACC CCA ATG ATG TCA   2328
Pro Val Asp Ser Asp Asp Leu Pro Leu Cys Ser Thr Pro Met Met Ser
                725                 730                 735

CCT GAC CAC CTC CAA GGC GAT GCA AGA GAG CAG CTA GAA AGC CTA ATG   2376
Pro Asp His Leu Gln Gly Asp Ala Arg Glu Gln Leu Glu Ser Leu Met
            740                 745                 750

CTC TCG GTG CTG CAG CAG AGC CTG AGT GGA CAG CCC CTG GAG AGC TGG   2424
Leu Ser Val Leu Gln Gln Ser Leu Ser Gly Gln Pro Leu Glu Ser Trp
        755                 760                 765

CCG AGG CCA GAG GTG GTC CTC GAG GGC TGC ACA CCC TCT GAG GAG GAG   2472
Pro Arg Pro Glu Val Val Leu Glu Gly Cys Thr Pro Ser Glu Glu Glu
    770                 775                 780

CAG CGG CAG TCG GTG CAG TCG GAC CAG GGC TAC ATC TCC AGG AGC TCC   2520
Gln Arg Gln Ser Val Gln Ser Asp Gln Gly Tyr Ile Ser Arg Ser Ser
785                 790                 795                 800

CCG CAG CCC CCC GAG TGG CTC ACG GAG GAG GAA GAG CTA GAA CTG GGT   2568
Pro Gln Pro Pro Glu Trp Leu Thr Glu Glu Glu Glu Leu Glu Leu Gly
                805                 810                 815

GAG CCC GTT GAG TCT CTC TCT CCT GAG GAA CTA CGG AGC CTG AGG AAG   2616
Glu Pro Val Glu Ser Leu Ser Pro Glu Glu Leu Arg Ser Leu Arg Lys
            820                 825                 830

CTC CAG AGG CAG CTT TTC TTC TGG GAG CTC GAG AAG AAC CCT GGC TGG   2664
Leu Gln Arg Gln Leu Phe Phe Trp Glu Leu Glu Lys Asn Pro Gly Trp
        835                 840                 845

AAC AGC TTG GAG CCA CGG AGA CCC ACC CCA GAA GAG CAG AAT CCC TCC   2712
Asn Ser Leu Glu Pro Arg Arg Pro Thr Pro Glu Glu Gln Asn Pro Ser
    850                 855                 860

TAG GCCTCCTGAG CCTGCTACTT AAGAGGGTGT ATATTGTACT CTGTGTGTGC         2765

GTGCGTGTGT GTGTGTGTGT GTGTGTGTGT GTGCGTGTGT GTGTGTGTGT GTGTGTGTGT  2825

GTGTGTGTAG TGCCCGGCTT AGAAATGTGA ACATCTGAAT CTGACATAGT GTTGTATACC  2885

TGAAGTCCCA GCACTTGGGA ACTGAGACTT GATGATCTCC TGAAGCCAGG TGTTCAGGGC  2945
```

```
CAGTGTGAAA ACATAGCAAG ACCTCAGAGA AATCAATGCA GACATCTTGG TACTGATCCC 3005
TAAACACACC CCTTTCCCTG ATAACCCGAC ATGAGCATCT GGTCATCATT GCACAAGAAT 3065
CCACAGCCCG TTCCCAGAGC TCATAGCCAA GTGTGTTGCT CATTCCTTGA ATATTTATTC 3125
TGTACCTACT ATTCATCAGA CATTTGGAAT TCAAAAACAA GTTACATGAC ACAGCCTTAG 3185
CCACTAAGAA GCTTAAAATT CGGTAAGGAT GTAAAATTAG CCAGGATGAA TAGAGGGCTG 3245
CTGCCCTGGC TGCAGAAGAG CAGGTCGTCT CGTTCCAGTC GAC                   3288
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 864 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
Met Ala Ile Arg Arg Cys Trp Pro Arg Val Val Pro Gly Pro Ala Leu
  1               5                  10                  15

Gly Trp Leu Leu Leu Leu Leu Asn Val Leu Ala Pro Gly Arg Ala Ser
             20                  25                  30

Pro Arg Leu Leu Asp Phe Pro Ala Pro Val Cys Ala Gln Glu Gly Leu
         35                  40                  45

Ser Cys Arg Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
     50                  55                  60

Pro Lys Asn Leu Thr Pro Ser Ser Pro Lys Asn Ile Tyr Ile Asn Leu
 65                  70                  75                  80

Ser Val Ser Ser Thr Gln His Gly Glu Leu Val Pro Val Leu His Val
                 85                  90                  95

Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
            100                 105                 110

Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Lys
        115                 120                 125

Phe Gln Phe Leu Ser Met Leu Gln His His Arg Lys Arg Trp Arg Phe
    130                 135                 140

Ser Phe Ser His Phe Val Val Asp Pro Gly Gln Glu Tyr Glu Val Thr
145                 150                 155                 160

Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Lys
                165                 170                 175

Ser Lys Ile Ile Phe Val Pro Asp Cys Glu Asp Ser Lys Met Lys Met
            180                 185                 190
```

```
Thr Thr Ser Cys Val Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
        195                 200                 205

Val Glu Thr Leu Asp Thr Gln His Leu Arg Val Asp Phe Thr Leu Trp
    210                 215                 220

Asn Glu Ser Thr Pro Tyr Gln Val Leu Leu Glu Ser Phe Ser Asp Ser
225                 230                 235                 240

Glu Asn His Ser Cys Phe Asp Val Val Lys Gln Ile Phe Ala Pro Arg
                245                 250                 255

Gln Glu Glu Phe His Gln Arg Ala Asn Val Thr Phe Thr Leu Ser Lys
            260                 265                 270

Phe His Trp Cys Cys His His His Val Gln Val Gln Pro Phe Phe Ser
        275                 280                 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ala Val Thr Val Pro Cys Pro
    290                 295                 300

Val Ile Ser Asn Thr Thr Val Pro Lys Pro Val Ala Asp Tyr Ile Pro
305                 310                 315                 320

Leu Trp Val Tyr Gly Leu Ile Thr Leu Ile Ala Ile Leu Leu Val Gly
                325                 330                 335

Ser Val Ile Val Leu Ile Ile Cys Met Thr Trp Arg Leu Ser Gly Ala
            340                 345                 350

Asp Gln Glu Lys His Gly Asp Asp Ser Lys Ile Asn Gly Ile Leu Pro
        355                 360                 365

Val Ala Asp Leu Thr Pro Pro Pro Leu Arg Pro Arg Lys Val Trp Ile
    370                 375                 380

Val Tyr Ser Ala Asp His Pro Leu Tyr Val Glu Val Val Leu Lys Phe
385                 390                 395                 400

Ala Gln Phe Leu Ile Thr Ala Cys Gly Thr Glu Val Ala Leu Asp Leu
                405                 410                 415

Leu Glu Glu Gln Val Ile Ser Glu Val Gly Val Met Thr Trp Val Ser
            420                 425                 430

Arg Gln Lys Gln Glu Met Val Glu Ser Asn Ser Lys Ile Ile Ile Leu
        435                 440                 445

Cys Ser Arg Gly Thr Gln Ala Lys Trp Lys Ala Ile Leu Gly Trp Ala
    450                 455                 460

Glu Pro Ala Val Gln Leu Arg Cys Asp His Trp Lys Pro Ala Gly Asp
465                 470                 475                 480

Leu Phe Thr Ala Ala Met Asn Met Ile Leu Pro Asp Phe Lys Arg Pro
                485                 490                 495

Ala Cys Phe Gly Thr Tyr Val Val Cys Tyr Phe Ser Gly Ile Cys Ser
            500                 505                 510
```

```
Glu Arg Asp Val Pro Asp Leu Phe Asn Ile Thr Ser Arg Tyr Pro Leu
        515                 520                 525

Met Asp Arg Phe Glu Glu Val Tyr Phe Arg Ile Gln Asp Leu Glu Met
    530                 535                 540

Phe Glu Pro Gly Arg Met His His Val Arg Glu Leu Thr Gly Asp Asn
545                 550                 555                 560

Tyr Leu Gln Ser Pro Ser Gly Arg Gln Leu Lys Glu Ala Val Leu Arg
                565                 570                 575

Phe Gln Glu Trp Gln Thr Gln Cys Pro Asp Trp Phe Glu Arg Glu Asn
            580                 585                 590

Leu Cys Leu Ala Asp Gly Gln Asp Leu Pro Ser Leu Asp Glu Glu Val
        595                 600                 605

Phe Glu Asp Pro Leu Leu Pro Pro Gly Gly Gly Ile Val Lys Gln Gln
    610                 615                 620

Pro Leu Val Arg Glu Leu Pro Ser Asp Gly Cys Leu Val Val Asp Val
625                 630                 635                 640

Cys Val Ser Glu Glu Glu Ser Arg Met Ala Lys Leu Asp Pro Gln Leu
                645                 650                 655

Trp Pro Gln Arg Glu Leu Val Ala His Thr Leu Gln Ser Met Val Leu
            660                 665                 670

Pro Ala Glu Gln Val Pro Ala Ala His Val Val Glu Pro Leu His Leu
        675                 680                 685

Pro Asp Gly Ser Gly Ala Ala Ala Gln Leu Pro Met Thr Glu Asp Ser
    690                 695                 700

Glu Ala Cys Pro Leu Leu Gly Val Gln Arg Asn Ser Ile Leu Cys Leu
705                 710                 715                 720

Pro Val Asp Ser Asp Asp Leu Pro Leu Cys Ser Thr Pro Met Met Ser
                725                 730                 735

Pro Asp His Leu Gln Gly Asp Ala Arg Glu Gln Leu Glu Ser Leu Met
            740                 745                 750

Leu Ser Val Leu Gln Gln Ser Leu Ser Gly Gln Pro Leu Glu Ser Trp
        755                 760                 765

Pro Arg Pro Glu Val Val Leu Glu Gly Cys Thr Pro Ser Glu Glu Glu
    770                 775                 780

Gln Arg Gln Ser Val Gln Ser Asp Gln Gly Tyr Ile Ser Arg Ser Ser
785                 790                 795                 800

Pro Gln Pro Pro Glu Trp Leu Thr Glu Glu Glu Glu Leu Glu Leu Gly
                805                 810                 815

Glu Pro Val Glu Ser Leu Ser Pro Glu Glu Leu Arg Ser Leu Arg Lys
            820                 825                 830
```

```
Leu Gln Arg Gln Leu Phe Phe Trp Glu Leu Glu Lys Asn Pro Gly Trp
        835                 840                 845

Asn Ser Leu Glu Pro Arg Arg Pro Thr Pro Glu Glu Gln Asn Pro Ser
    850                 855                 860
```

(2) INFORMATION FOR SEQ ID NO:3:

```
    (i) SEQUENCE CHARACTERISTICS:
         (A) LENGTH: 3223 base pairs
         (B) TYPE: nucleic acid
         (C) STRANDEDNESS: single
         (D) TOPOLOGY: linear

   (ii) MOLECULE TYPE: cDNA to mRNA

  (iii) HYPOTHETICAL: NO

   (iv) ANTI-SENSE: NO

   (vi) ORIGINAL SOURCE:
         (A) ORGANISM: Human
         (B) CLONE: IL-17R

   (ix) FEATURE:
         (A) NAME/KEY: CDS
         (B) LOCATION: 93..2690

   (xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:
```

```
GGGAGACCGG AATTCCGGGA AAAGAAAGCC TCAGAACGTT CGCTCGCTGC GTCCCCAGCC      60

GGGGCCGAGC CCTCCGCGAC GCCACCCGGG CC ATG GGG GCC GCA CGC AGC CCG       113
                                    Met Gly Ala Ala Arg Ser Pro
                                      1               5

CCG TCC GCT GTC CCG GGG CCC CTG CTG GGG CTC CTC CTG CTG CTC CTG       161
Pro Ser Ala Val Pro Gly Pro Leu Leu Gly Leu Leu Leu Leu Leu Leu
         10                  15                  20

GGC GTG CTG GCC CCG GGT GGC GCC TCC CTG CGA CTC CTG GAC CAC CGG       209
Gly Val Leu Ala Pro Gly Gly Ala Ser Leu Arg Leu Leu Asp His Arg
     25                  30                  35

GCG CTG GTC TGC TCC CAG CCG GGG CTA AAC TGC ACG GTC AAG AAT AGT       257
Ala Leu Val Cys Ser Gln Pro Gly Leu Asn Cys Thr Val Lys Asn Ser
 40                  45                  50                  55

ACC TGC CTG GAT GAC AGC TGG ATT CAC CCT CGA AAC CTG ACC CCC TCC       305
Thr Cys Leu Asp Asp Ser Trp Ile His Pro Arg Asn Leu Thr Pro Ser
                 60                  65                  70

TCC CCA AAG GAC CTG CAG ATC CAG CTG CAC TTT GCC CAC ACC CAA CAA       353
Ser Pro Lys Asp Leu Gln Ile Gln Leu His Phe Ala His Thr Gln Gln
             75                  80                  85
```

```
GGA GAC CTG TTC CCC GTG GCT CAC ATC GAA TGG ACA CTG CAG ACA GAC      401
Gly Asp Leu Phe Pro Val Ala His Ile Glu Trp Thr Leu Gln Thr Asp
        90                  95                  100

GCC AGC ATC CTG TAC CTC GAG GGT GCA GAG TTA TCT GTC CTG CAG CTG      449
Ala Ser Ile Leu Tyr Leu Glu Gly Ala Glu Leu Ser Val Leu Gln Leu
    105                 110                 115

AAC ACC AAT GAA CGT TTG TGC GTC AGG TTT GAG TTT CTG TCC AAA CTG      497
Asn Thr Asn Glu Arg Leu Cys Val Arg Phe Glu Phe Leu Ser Lys Leu
120                 125                 130                 135

AGG CAT CAC CAC AGG CGG TGG CGT TTT ACC TTC AGC CAC TTT GTG GTT      545
Arg His His His Arg Arg Trp Arg Phe Thr Phe Ser His Phe Val Val
                140                 145                 150

GAC CCT GAC CAG GAA TAT GAG GTG ACC GTT CAC CAC CTG CCC AAG CCC      593
Asp Pro Asp Gln Glu Tyr Glu Val Thr Val His His Leu Pro Lys Pro
            155                 160                 165

ATC CCT GAT GGG GAC CCA AAC CAC CAG TCC AAG AAT TTC CTT GTG CCT      641
Ile Pro Asp Gly Asp Pro Asn His Gln Ser Lys Asn Phe Leu Val Pro
        170                 175                 180

GAC TGT GAG CAC GCC AGG ATG AAG GTA ACC ACG CCA TGC ATG AGC TCA      689
Asp Cys Glu His Ala Arg Met Lys Val Thr Thr Pro Cys Met Ser Ser
    185                 190                 195

GGC AGC CTG TGG GAC CCC AAC ATC ACC GTG GAG ACC CTG GAG GCC CAC      737
Gly Ser Leu Trp Asp Pro Asn Ile Thr Val Glu Thr Leu Glu Ala His
200                 205                 210                 215

CAG CTG CGT GTG AGC TTC ACC CTG TGG AAC GAA TCT ACC CAT TAC CAG      785
Gln Leu Arg Val Ser Phe Thr Leu Trp Asn Glu Ser Thr His Tyr Gln
                220                 225                 230

ATC CTG CTG ACC AGT TTT CCG CAC ATG GAG AAC CAC AGT TGC TTT GAG      833
Ile Leu Leu Thr Ser Phe Pro His Met Glu Asn His Ser Cys Phe Glu
            235                 240                 245

CAC ATG CAC CAC ATA CCT GCG CCC AGA CCA GAA GAG TTC CAC CAG CGA      881
His Met His His Ile Pro Ala Pro Arg Pro Glu Glu Phe His Gln Arg
        250                 255                 260

TCC AAC GTC ACA CTC ACT CTA CGC AAC CTT AAA GGG TGC TGT CGC CAC      929
Ser Asn Val Thr Leu Thr Leu Arg Asn Leu Lys Gly Cys Cys Arg His
    265                 270                 275

CAA GTG CAG ATC CAG CCC TTC TTC AGC AGC TGC CTC AAT GAC TGC CTC      977
Gln Val Gln Ile Gln Pro Phe Phe Ser Ser Cys Leu Asn Asp Cys Leu
280                 285                 290                 295

AGA CAC TCC GCG ACT GTT TCC TGC CCA GAA ATG CCA GAC ACT CCA GAA     1025
Arg His Ser Ala Thr Val Ser Cys Pro Glu Met Pro Asp Thr Pro Glu
                300                 305                 310

CCA ATT CCG GAC TAC ATG CCC CTG TGG GTG TAC TGG TTC ATC ACG GGC     1073
Pro Ile Pro Asp Tyr Met Pro Leu Trp Val Tyr Trp Phe Ile Thr Gly
            315                 320                 325
```

```
ATC TCC ATC CTG CTG GTG GGC TCC GTC ATC CTG CTC ATC GTC TGC ATG   1121
Ile Ser Ile Leu Leu Val Gly Ser Val Ile Leu Leu Ile Val Cys Met
        330                 335                 340

ACC TGG AGG CTA GCT GGG CCT GGA AGT GAA AAA TAC AGT GAT GAC ACC   1169
Thr Trp Arg Leu Ala Gly Pro Gly Ser Glu Lys Tyr Ser Asp Asp Thr
    345                 350                 355

AAA TAC ACC GAT GGC CTG CCT GCG GCT GAC CTG ATC CCC CCA CCG CTG   1217
Lys Tyr Thr Asp Gly Leu Pro Ala Ala Asp Leu Ile Pro Pro Pro Leu
360                 365                 370                 375

AAG CCC AGG AAG GTC TGG ATC ATC TAC TCA GCC GAC CAC CCC CTC TAC   1265
Lys Pro Arg Lys Val Trp Ile Ile Tyr Ser Ala Asp His Pro Leu Tyr
                380                 385                 390

GTG GAC GTG GTC CTG AAA TTC GCC CAG TTC CTG CTC ACC GCC TGC GGC   1313
Val Asp Val Val Leu Lys Phe Ala Gln Phe Leu Leu Thr Ala Cys Gly
            395                 400                 405

ACG GAA GTG GCC CTG GAC CTG CTG GAA GAG CAG GCC ATC TCG GAG GCA   1361
Thr Glu Val Ala Leu Asp Leu Leu Glu Glu Gln Ala Ile Ser Glu Ala
        410                 415                 420

GGA GTC ATG ACC TGG GTG GGC CGT CAG AAG CAG GAG ATG GTG GAG AGC   1409
Gly Val Met Thr Trp Val Gly Arg Gln Lys Gln Glu Met Val Glu Ser
    425                 430                 435

AAC TCT AAG ATC ATC GTC CTG TGC TCC CGC GGC ACG CGC GCC AAG TGG   1457
Asn Ser Lys Ile Ile Val Leu Cys Ser Arg Gly Thr Arg Ala Lys Trp
440                 445                 450                 455

CAG GCG CTC CTG GGC CGG GGG GCG CCT GTG CGG CTG CGC TGC GAC CAC   1505
Gln Ala Leu Leu Gly Arg Gly Ala Pro Val Arg Leu Arg Cys Asp His
                460                 465                 470

GGA AAG CCC GTG GGG GAC CTG TTC ACT GCA GCC ATG AAC ATG ATC CTC   1553
Gly Lys Pro Val Gly Asp Leu Phe Thr Ala Ala Met Asn Met Ile Leu
            475                 480                 485

CCG GAC TTC AAG AGG CCA GCC TGC TTC GGC ACC TAC GTA GTC TGC TAC   1601
Pro Asp Phe Lys Arg Pro Ala Cys Phe Gly Thr Tyr Val Val Cys Tyr
        490                 495                 500

TTC AGC GAG GTC AGC TGT GAC GGC GAC GTC CCC GAC CTG TTC GGC GCG   1649
Phe Ser Glu Val Ser Cys Asp Gly Asp Val Pro Asp Leu Phe Gly Ala
    505                 510                 515

GCG CCG CGG TAC CCG CTC ATG GAC AGG TTC GAG GAG GTG TAC TTC CGC   1697
Ala Pro Arg Tyr Pro Leu Met Asp Arg Phe Glu Glu Val Tyr Phe Arg
520                 525                 530                 535

ATC CAG GAC CTG GAG ATG TTC CAG CCG GGC CGC ATG CAC CGC GTA GGG   1745
Ile Gln Asp Leu Glu Met Phe Gln Pro Gly Arg Met His Arg Val Gly
                540                 545                 550

GAG CTG TCG GGG GAC AAC TAC CTG CGG AGC CCG GGC GGC AGG CAG CTC   1793
Glu Leu Ser Gly Asp Asn Tyr Leu Arg Ser Pro Gly Gly Arg Gln Leu
            555                 560                 565
```

```
CGC GCC GCC CTG GAC AGG TTC CGG GAC TGG CAG GTC CGC TGT CCC GAC   1841
Arg Ala Ala Leu Asp Arg Phe Arg Asp Trp Gln Val Arg Cys Pro Asp
        570                 575                 580

TGG TTC GAA TGT GAG AAC CTC TAC TCA GCA GAT GAC CAG GAT GCC CCG   1889
Trp Phe Glu Cys Glu Asn Leu Tyr Ser Ala Asp Asp Gln Asp Ala Pro
    585                 590                 595

TCC CTG GAC GAA GAG GTG TTT GAG GAG CCA CTG CTG CCT CCG GGA ACC   1937
Ser Leu Asp Glu Glu Val Phe Glu Glu Pro Leu Leu Pro Pro Gly Thr
600                 605                 610                 615

GGC ATC GTG AAG CGG GCG CCC CTG GTG CGC GAG CCT GGC TCC CAG GCC   1985
Gly Ile Val Lys Arg Ala Pro Leu Val Arg Glu Pro Gly Ser Gln Ala
                620                 625                 630

TGC CTG GCC ATA GAC CCG CTG GTC GGG GAG GAA GGA GGA GCA GCA GTG   2033
Cys Leu Ala Ile Asp Pro Leu Val Gly Glu Glu Gly Gly Ala Ala Val
            635                 640                 645

GCA AAG CTG GAA CCT CAC CTG CAG CCC CGG GGT CAG CCA GCG CCG CAG   2081
Ala Lys Leu Glu Pro His Leu Gln Pro Arg Gly Gln Pro Ala Pro Gln
        650                 655                 660

CCC CTC CAC ACC CTG GTG CTC GCC GCA GAG GAG GGG GCC CTG GTG GCC   2129
Pro Leu His Thr Leu Val Leu Ala Ala Glu Glu Gly Ala Leu Val Ala
    665                 670                 675

GCG GTG GAG CCT GGG CCC CTG GCT GAC GGT GCC GCA GTC CGG CTG GCA   2177
Ala Val Glu Pro Gly Pro Leu Ala Asp Gly Ala Ala Val Arg Leu Ala
680                 685                 690                 695

CTG GCG GGG GAG GGC GAG GCC TGC CCG CTG CTG GGC AGC CCG GGC GCT   2225
Leu Ala Gly Glu Gly Glu Ala Cys Pro Leu Leu Gly Ser Pro Gly Ala
                700                 705                 710

GGG CGA AAT AGC GTC CTC TTC CTC CCC GTG GAC CCC GAG GAC TCG CCC   2273
Gly Arg Asn Ser Val Leu Phe Leu Pro Val Asp Pro Glu Asp Ser Pro
            715                 720                 725

CTT GGC AGC AGC ACC CCC ATG GCG TCT CCT GAC CTC CTT CCA GAG GAC   2321
Leu Gly Ser Ser Thr Pro Met Ala Ser Pro Asp Leu Leu Pro Glu Asp
        730                 735                 740

GTG AGG GAG CAC CTC GAA GGC TTG ATG CTC TCG CTC TTC GAG CAG AGT   2369
Val Arg Glu His Leu Glu Gly Leu Met Leu Ser Leu Phe Glu Gln Ser
    745                 750                 755

CTG AGC TGC CAG GCC CAG GGG GGC TGC AGT AGA CCC GCC ATG GTC CTC   2417
Leu Ser Cys Gln Ala Gln Gly Gly Cys Ser Arg Pro Ala Met Val Leu
760                 765                 770                 775

ACA GAC CCA CAC ACG CCC TAC GAG GAG GAG CAG CGG CAG TCA GTG CAG   2465
Thr Asp Pro His Thr Pro Tyr Glu Glu Glu Gln Arg Gln Ser Val Gln
                780                 785                 790

TCT GAC CAG GGC TAC ATC TCC AGG AGC TCC CCG CAG CCC CCC GAG GGA   2513
Ser Asp Gln Gly Tyr Ile Ser Arg Ser Ser Pro Gln Pro Pro Glu Gly
            795                 800                 805
```

```
CTC ACG GAA ATG GAG GAA GAG GAG GAA GAG GAG CAG GAC CCA GGG AAG    2561
Leu Thr Glu Met Glu Glu Glu Glu Glu Glu Glu Gln Asp Pro Gly Lys
        810                 815                 820

CCG GCC CTG CCA CTC TCT CCC GAG GAC CTG GAG AGC CTG AGG AGC CTC    2609
Pro Ala Leu Pro Leu Ser Pro Glu Asp Leu Glu Ser Leu Arg Ser Leu
    825                 830                 835

CAG CGG CAG CTG CTT TTC CGC CAG CTG CAG AAG AAC TCG GGC TGG GAC    2657
Gln Arg Gln Leu Leu Phe Arg Gln Leu Gln Lys Asn Ser Gly Trp Asp
840                 845                 850                 855

ACG ATG GGG TCA GAG TCA GAG GGG CCC AGT GCA TGA GGGCGGCTCC         2703
Thr Met Gly Ser Glu Ser Glu Gly Pro Ser Ala
                860                 865

CCAGGGACCG CCCAGATCCC AGCTTTGAGA GAGGAGTGTG TGTGCACGTA TTCATCTGTG 2763

TGTACATGTC TGCATGTGTA TATGTTCGTG TGTGAAATGT AGGCTTTAAA ATGTAAATGT 2823

CTGGATTTTA ATCCCAGGCA TCCCTCCTAA CTTTTCTTTG TGCAGCGGTC TGGTTATCGT 2883

CTATCCCCAG GGGAATCCAC ACAGCCCGCT CCCAGGAGCT AATGGTAGAG CGTCCTTGAG 2943

GCTCCATTAT TCGTTCATTC AGCATTTATT GTGCACCTAC TATGTGGCGG GCATTTGGGA 3003

TACCAAGATA AATTGCATGC GGCATGGCCC CAGCCATGAA GGAACTTAAC CGCTAGTGCC 3063

GAGGACACGT TAAACGAACA GGATGGGCCG GGCACGGTGG CTCACGCCTG TAATCCCAGC 3123

ACACTGGGAG GCCGAGGCAG GTGGATCACT CTGAGGTCAG GAGTTTGAGC CAGCCTGGCC 3183

AACATGGTGA AACCCCGGAA TTCGAGCTCG GTACCCGGGG                       3223
```

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 866 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

```
Met Gly Ala Ala Arg Ser Pro Pro Ser Ala Val Pro Gly Pro Leu Leu
 1               5                  10                  15

Gly Leu Leu Leu Leu Leu Leu Gly Val Leu Ala Pro Gly Gly Ala Ser
            20                  25                  30

Leu Arg Leu Leu Asp His Arg Ala Leu Val Cys Ser Gln Pro Gly Leu
        35                  40                  45

Asn Cys Thr Val Lys Asn Ser Thr Cys Leu Asp Asp Ser Trp Ile His
    50                  55                  60

Pro Arg Asn Leu Thr Pro Ser Ser Pro Lys Asp Leu Gln Ile Gln Leu
65                  70                  75                  80
```

```
His Phe Ala His Thr Gln Gln Gly Asp Leu Phe Pro Val Ala His Ile
                85                  90                  95

Glu Trp Thr Leu Gln Thr Asp Ala Ser Ile Leu Tyr Leu Glu Gly Ala
            100                 105                 110

Glu Leu Ser Val Leu Gln Leu Asn Thr Asn Glu Arg Leu Cys Val Arg
        115                 120                 125

Phe Glu Phe Leu Ser Lys Leu Arg His His His Arg Arg Trp Arg Phe
    130                 135                 140

Thr Phe Ser His Phe Val Val Asp Pro Asp Gln Glu Tyr Glu Val Thr
145                 150                 155                 160

Val His His Leu Pro Lys Pro Ile Pro Asp Gly Asp Pro Asn His Gln
                165                 170                 175

Ser Lys Asn Phe Leu Val Pro Asp Cys Glu His Ala Arg Met Lys Val
            180                 185                 190

Thr Thr Pro Cys Met Ser Ser Gly Ser Leu Trp Asp Pro Asn Ile Thr
        195                 200                 205

Val Glu Thr Leu Glu Ala His Gln Leu Arg Val Ser Phe Thr Leu Trp
    210                 215                 220

Asn Glu Ser Thr His Tyr Gln Ile Leu Leu Thr Ser Phe Pro His Met
225                 230                 235                 240

Glu Asn His Ser Cys Phe Glu His Met His His Ile Pro Ala Pro Arg
                245                 250                 255

Pro Glu Glu Phe His Gln Arg Ser Asn Val Thr Leu Thr Leu Arg Asn
            260                 265                 270

Leu Lys Gly Cys Cys Arg His Gln Val Gln Ile Gln Pro Phe Phe Ser
        275                 280                 285

Ser Cys Leu Asn Asp Cys Leu Arg His Ser Ala Thr Val Ser Cys Pro
    290                 295                 300

Glu Met Pro Asp Thr Pro Glu Pro Ile Pro Asp Tyr Met Pro Leu Trp
305                 310                 315                 320

Val Tyr Trp Phe Ile Thr Gly Ile Ser Ile Leu Leu Val Gly Ser Val
                325                 330                 335

Ile Leu Leu Ile Val Cys Met Thr Trp Arg Leu Ala Gly Pro Gly Ser
            340                 345                 350

Glu Lys Tyr Ser Asp Asp Thr Lys Tyr Thr Asp Gly Leu Pro Ala Ala
        355                 360                 365

Asp Leu Ile Pro Pro Pro Leu Lys Pro Arg Lys Val Trp Ile Ile Tyr
    370                 375                 380

Ser Ala Asp His Pro Leu Tyr Val Asp Val Val Leu Lys Phe Ala Gln
385                 390                 395                 400
```

```
Phe Leu Leu Thr Ala Cys Gly Thr Glu Val Ala Leu Asp Leu Leu Glu
                405                 410                 415

Glu Gln Ala Ile Ser Glu Ala Gly Val Met Thr Trp Val Gly Arg Gln
            420                 425                 430

Lys Gln Glu Met Val Glu Ser Asn Ser Lys Ile Ile Val Leu Cys Ser
        435                 440                 445

Arg Gly Thr Arg Ala Lys Trp Gln Ala Leu Leu Gly Arg Gly Ala Pro
    450                 455                 460

Val Arg Leu Arg Cys Asp His Gly Lys Pro Val Gly Asp Leu Phe Thr
465                 470                 475                 480

Ala Ala Met Asn Met Ile Leu Pro Asp Phe Lys Arg Pro Ala Cys Phe
                485                 490                 495

Gly Thr Tyr Val Val Cys Tyr Phe Ser Glu Val Ser Cys Asp Gly Asp
            500                 505                 510

Val Pro Asp Leu Phe Gly Ala Ala Pro Arg Tyr Pro Leu Met Asp Arg
        515                 520                 525

Phe Glu Glu Val Tyr Phe Arg Ile Gln Asp Leu Glu Met Phe Gln Pro
    530                 535                 540

Gly Arg Met His Arg Val Gly Glu Leu Ser Gly Asp Asn Tyr Leu Arg
545                 550                 555                 560

Ser Pro Gly Gly Arg Gln Leu Arg Ala Ala Leu Asp Arg Phe Arg Asp
                565                 570                 575

Trp Gln Val Arg Cys Pro Asp Trp Phe Glu Cys Glu Asn Leu Tyr Ser
            580                 585                 590

Ala Asp Asp Gln Asp Ala Pro Ser Leu Asp Glu Glu Val Phe Glu Glu
        595                 600                 605

Pro Leu Leu Pro Pro Gly Thr Gly Ile Val Lys Arg Ala Pro Leu Val
    610                 615                 620

Arg Glu Pro Gly Ser Gln Ala Cys Leu Ala Ile Asp Pro Leu Val Gly
625                 630                 635                 640

Glu Glu Gly Gly Ala Ala Val Ala Lys Leu Glu Pro His Leu Gln Pro
                645                 650                 655

Arg Gly Gln Pro Ala Pro Gln Pro Leu His Thr Leu Val Leu Ala Ala
            660                 665                 670

Glu Glu Gly Ala Leu Val Ala Ala Val Glu Pro Gly Pro Leu Ala Asp
        675                 680                 685

Gly Ala Ala Val Arg Leu Ala Leu Ala Gly Glu Gly Glu Ala Cys Pro
    690                 695                 700

Leu Leu Gly Ser Pro Gly Ala Gly Arg Asn Ser Val Leu Phe Leu Pro
705                 710                 715                 720
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Val Asp Pro Glu Asp Ser Pro Leu Gly Ser Ser Thr Pro Met Ala Ser
                725                 730                 735

Pro Asp Leu Leu Pro Glu Asp Val Arg Glu His Leu Glu Gly Leu Met
            740                 745                 750

Leu Ser Leu Phe Glu Gln Ser Leu Ser Cys Gln Ala Gln Gly Gly Cys
        755                 760                 765

Ser Arg Pro Ala Met Val Leu Thr Asp Pro His Thr Pro Tyr Glu Glu
    770                 775                 780

Glu Gln Arg Gln Ser Val Gln Ser Asp Gln Gly Tyr Ile Ser Arg Ser
785                 790                 795                 800

Ser Pro Gln Pro Pro Glu Gly Leu Thr Glu Met Glu Glu Glu Glu Glu
                805                 810                 815

Glu Glu Gln Asp Pro Gly Lys Pro Ala Leu Pro Leu Ser Pro Glu Asp
            820                 825                 830

Leu Glu Ser Leu Arg Ser Leu Gln Arg Gln Leu Leu Phe Arg Gln Leu
        835                 840                 845

Gln Lys Asn Ser Gly Trp Asp Thr Met Gly Ser Glu Ser Glu Gly Pro
    850                 855                 860

Ser Ala
865
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CLAIMS

We claim:

1. A method for reducing the amount of nitric oxide produced by a cartilage associated cell, comprising contacting the cell with a soluble Interleukin-17 receptor (IL-17R).

2. The method according to claim 1, wherein the soluble IL-17R is selected from the group consisting of:

(a) a protein comprising amino acids 1 through 322 of SEQ ID NO.: 2;

(b) a protein comprising amino acids 1 through 320 of SEQ ID NO.: 4;

(c) a protein having an amino acid sequence that is at least about 70% identical to the amino acid sequences of the proteins of (a) or (b), and that binds IL-17; and

(d) fragments of the proteins of (a), (b), or (c), that bind IL-17.

3. A composition for regulation of nitric oxide levels, comprising a soluble IL-17 receptor and a pharmaceutically acceptable carrier or diluent.

4. The composition according to claim 3, wherein the soluble IL-17 receptor is selected from the group consisting of:

(a) a protein comprising amino acids 1 through 322 of SEQ ID NO.: 2;

(b) a protein comprising amino acids 1 through 320 of SEQ ID NO.: 4;

(c) a protein having an amino acid sequence that is at least about 70% identical to the amino acid sequences of the proteins of (a) or (b), and that binds IL-17; and

(d) fragments of the proteins of (a), (b), or (c), that bind IL-17.

5. The composition according to claim 3, further comprising an immunoregulatory molecule selected from the group consisting of a soluble Type I IL-1 receptor, a soluble Type II IL-1 receptor, an IL-1 receptor antagonist, a soluble TNF receptor, a fusion protein comprising an IL-1 receptor and a TNF receptor, and combinations thereof.

6. The composition according to claim 4, further comprising an immunoregulatory molecule selected from the group consisting of a soluble Type I IL-1 receptor, a soluble Type II IL-1 receptor, an IL-1 receptor antagonist, a soluble TNF receptor, a fusion protein comprising an IL-1 receptor and a TNF receptor, and combinations thereof.

7. The method according to claim 1, wherein the cell is simultaneously, sequentially or separately contacted with an immunoregulatory molecule selected from the

group consisting of a soluble Type I IL-1 receptor, a soluble Type II IL-1 receptor, an IL-1 receptor antagonist, a soluble TNF receptor, a fusion protein comprising an IL-1 receptor and a TNF receptor, and combinations thereof.

8. The method according to claim 2, wherein the cell is simultaneously, sequentially or separately contacted with an immunoregulatory molecule selected from the group consisting of a soluble Type I IL-1 receptor, a soluble Type II IL-1 receptor, an IL-1 receptor antagonist, a soluble TNF receptor, a fusion protein comprising an IL-1 receptor and a TNF receptor, and combinations thereof.

9. A method of treating osteoarthritis in an individual, comprising administering to the individual an amount of soluble IL-17 receptor sufficient to reduce the level of nitric oxide produced by cartilage-associated cells, in a pharmaceutically acceptable carrier or diluent.

10. The method according to claim 9, wherein the soluble IL-17 receptor is administered simultaneously, sequentially or separately with an immunoregulatory molecule selected from the group consisting of a soluble Type I IL-1 receptor, a soluble Type II IL-1 receptor, an IL-1 receptor antagonist, a soluble TNF receptor, a fusion protein comprising an IL-1 receptor and a TNF receptor, and combinations thereof.

11. The method according to clam 9, wherein the soluble IL-17 receptor is selected from the group consisting of:

(a) a protein comprising amino acids 1 through 322 of SEQ ID NO.: 2;

(b) a protein comprising amino acids 1 through 320 of SEQ ID NO.: 4;

(c) a protein having an amino acid sequence that is at least about 70% identical to the amino acid sequences of the proteins of (a) or (b), and that binds IL-17; and

(d) fragments of the proteins of (a), (b), or (c), that bind IL-17.

12. The method according to claim 11, wherein the soluble IL-17 receptor is administered simultaneously, sequentially or separately with an immunoregulatory molecule selected from the group consisting of a soluble Type I IL-1 receptor, a soluble Type II IL-1 receptor, an IL-1 receptor antagonist, a soluble TNF receptor, a fusion protein comprising an IL-1 receptor and a TNF receptor, and combinations thereof.

13. A method of preparing a medication for adminstration to a mammal afflicted with osteoarthritis, comprising formulating a soluble IL-17 receptor in a suitable excipient or carrier.

14. The method of claim 13, wherein the soluble IL-17 receptor is selected from the group consisting of:

(a) a protein comprising amino acids 1 through 322 of SEQ ID NO.: 2;

(b) a protein comprising amino acids 1 through 320 of SEQ ID NO.: 4;

(c) a protein having an amino acid sequence that is at least about 70% identical to the amino acid sequences of the proteins of (a) or (b), and that binds IL-17; and

(d) fragments of the proteins of (a), (b), or (c), that bind IL-17.

15. The method according to claim 13 or claim 14, wherein the medication further comprises an immunoregulatory molecule selected from the group consisting of a soluble Type I IL-1 receptor, a soluble Type II IL-1 receptor, an IL-1 receptor antagonist, a soluble TNF receptor, a fusion protein comprising an IL-1 receptor and a TNF receptor, and combinations thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/21451

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) : A61K 38/19, 38/00
US CL : 514/ 2, 8, 12, 21
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/ 2, 8, 12, 21

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
(IL-17 or CTLA) and receptor, and (treat or inhibit or reduce or alleviate) and (free radical or nitric oxide or arthritis or cartilage or inflammation)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----- Y	WO 96/29408 A1 (IMMUNEX CORPORATION) 26 SEPTEMBER 1996, see the claims and pages 1-15.	1-2, 7-12 ----- 3-6, 13-15
X --- Y	YAO et al. Herpesvirus saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. Immunity, 1995, Vol. 3, see pages 811-821.	1-2, 7-12 ----- 3-6, 13-15
Y, P	ATTUR et al. Interleukin-17 up-regulation of nitric oxide production in human osteoarthritis cartilage. Arthritis and Rheumatism, 1997, Vol. 40, No. 6, see pages 1050-1053.	3-6, 13-15

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"B" earlier document published on or after the international filing date
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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	LOTZ et al. IL-17 promotes cartilage degradation. Arthritis and Rheumatism, 1996, Vol. 39, No. (9 suppl.), see page S120.	3-6, 13-15
Y,P	SPRIGGS M. Interleukin-17 and its receptor. J. Clin. Immunol., 1997, Vol. 17, No. 5, see pages 366-369.	1-15
Y	YAO e al. Complete nucleotide sequence of the mouse CTLA-8 gene. Gene, 1996, Vol. 168, No. 2, see pages 223-225.	1-2, 7-12
Y	YAO et al. Human IL-17: A novel cytokine derived from T cells. J. Immunol., 1995, Vol. 155, No. 12, see pages 5483-5486.	1-2, 7-12
A	FOSSIEZ et al. T cell Interleukin-17 induces stromal cells to produce proinflammatory ad hematopoetic cytokines. J. Exp. Med., June 1996, Vol. 183, see pages 2593-2603.	1-15